Local Application Of The Sympathetic Nerve Blocker Around The Dorsal Root Ganglion Reduces Painful Behavior In A Lumbar Radiculopathy Model

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Introduction: Lumbar radicular pain associated with lumbar disc herniation and lumbar spinal canal stenosis is one of the most common symptoms treated by orthopaedic surgeons. Recently, the sympathetic nervous system is considered to be involved in causing lumbar radicular pain. In our previous studies, we reported that spinal nerve root constriction induced sympathetic sprouting around dorsal root ganglion (DRG) neurons. Also, our electrophysiological analysis showed that norepinephrine released from postganglionic neurons in the sympathetic nervous system, enhanced the excitability of the DRG neurons. In addition, surgical sympathectomy reduced pain-related behavior and hyperexcitability of DRG neurons caused by spinal nerve root constriction. Accordingly, pain mechanism through the sympathetic nervous system is complicated in DRG neurons.

A number of sympathetic nerve blockers appeared and are expected to regulate the sympathetically maintained pain. In some previous studies, analgesic effects of sympathetic nerve blocker in the rats with nerve injury were variable due to systemic administration. However, it is difficult to apply drugs on DRG neurons directly. We developed unique drug delivery system on DRG neurons with fine polyethylene catheter.

The purpose of the present study is to introduce our drug delivery system on DRG neurons and to examine the effects of sympathetic nerve blocker in the rats with spinal nerve root constriction using behavioral study.

Methods: The experimental protocols used in this study were approved by the Animal Care and Use Committee of our university. We used a total of 80 adult male Sprague-Dawley rats weighing 150-200g at the beginning of the study. The left L5 spinal root was ligated proximal to the DRG to produce models of lumbar radiculopathy. Just after root constriction, a polyethylene catheter (PE-10: inner diameter 0.28mm, outer diameter 0.61mm) was placed above the left L5 DRG and fixed with 4-0 nylon at the level of L6-S fascia. Then the catheter was transferred to cranial side subcutaneously, put outside the body at C6-7 level and applied to administer the sympathetic nerve blocker from the tip. We administered phentolamine (non-selective α-adrenoceptor antagonist: n=10), prazosin (α1-adrenoceptor antagonist: n=10) and yohimbine (α2-adrenoceptor: n=10) at each concentration of 100mM for 3 consecutive days after ligation at a dose of 100μl/kg. We also administered silodosin (α1a-adrenoceptor antagonist: n=10) at a concentration of 100mM for 3 consecutive days after ligation at a dose of 100μl/kg to confirm the selectivity property of α1-adrenoceptor antagonist. In addition, we administered phentolamine at a concentration of 100mM for 3 consecutive days from fourth post-operative day at a dose of 100μl/kg to investigate whether sympathetic nerve blocker affects after generation of painful behavior (n=10). Control rats received vehicle injections of each sympathetic nerve blocker (n=30).
To evaluate the pain relief effect of sympathetic nerve blocker, we conducted behavioral analysis using the mechanical and thermal withdrawal response. The mechanical withdrawal response was examined by a stimulus of 3.8g using von Frey filaments. The right and left hind paw was stimulated a total of thirty times. The mechanical withdrawal frequency was obtained as the number of responses from the left side subtracted from the number of responses from the right side. The thermal withdrawal response was measured by a radiant heat source. Each hind paw was tested five times and the mean withdrawal latency was calculated. The thermal withdrawal latency was defined as left-right asymmetry of the latency. Behavioral tests were performed two days before the operation and on the third, seventh, tenth, 14th, 21st and 28th post-operative day.

Statistical analysis of the data was performed by Student’s t-test. P<0.05 was statistically considered significant.

**Results:** Phentolamine and yohimbine reduced mechanical allodynia and thermal hyperalgesia for 28 days. Pain analgesic effect of yohimbine was stronger than that of phentolamine. prazosin relieved painful behavior almost all experimental periods, however, the effect was weaker than that of phentolamine and yohimbine. In contrast, silodosin had no pain analgesic effect. (Figs. 1)

When the first drug injection started at fourth post-operative, the mechanical allodynia that once generated at third post-operative day had been attenuated until the 28th post-operative day with phentolamine compared to control group (Fig. 2). Similarly, phentolamine had been effective against thermal hyperalgesia (data not shown).

**Discussion:** The present study showed that sympathetic nerve blocker attenuated the pain-related behavior caused by spinal nerve root constriction. These mechanisms may be based on α2-adrenoceptor, because the selectivity to α1-adrenoceptor of silodosin was too strong to relieve the pain-related behavior. We note that the selectivity to α1-adrenoceptor of prazosin was weak compared to silodosin, so prazosin was effective to reduce painful behavior. Sympathetic nerve blockers were effective after generation of painful behavior. So we consider that sympathetic nerve blockade via α2-adrenoceptor may contribute to pain relief in neuropathic pain.

**Significance:** The sympathetic nervous system was closely associated with lumbar radicular pain, and suppressing the activity of the sympathetic nervous system may therefore lead to pain relief.
Fig. 1. a) Withdrawal frequency and b) withdrawal latency when phentolamine, prazosin and yohimbine were administered for 3 days from operative day (marked with ▲). Error bars denote the standard deviation of the mean (* p < 0.05 versus phentolamine; † p < 0.05 versus prazosin; ‡ p < 0.05 versus yohimbine).
Fig. 2. Withdrawal frequency when phentolamine was administered for 3 days from fourth post-operative day (marked with ▲). Error bars denote the standard deviation of the mean (* p < 0.05 versus phentolamine).